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Remarks:
This application was filed on 01 - 04 - 1999 as a divisional application to the application mentioned under INID code 62.

(54) Transesterification products of corn oil and glycerol and their use in pharmaceutical compositions

(57) Transesterification products of corn oil and glycerol having a total palmitic acid and stearic acid content of mono-, di- and tri-glycerides of less than 10% by weight, and a free glycerol content of less than 10 % by weight. Use of these products in pharmaceutical compositions.

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Table (continued)

Bioavailability of Ciclosporin in Humans			
Mean (±SD) values of $AUC_{(0-48\ h)}$, C_{max} and T_{max} after single oral administration of different dosages of Composition X and Composition 8			
400 mg Comp X	3326 ± 1115	785 ± 252	2.1 ± 0.9
400 mg Comp 8	6944 ± 1468	1557 ± 286	1.4 ± 0.4
600 mg Comp X	4501 ± 1217	917 ± 236	2.3 ± 1.0
600 mg Comp 8	9689 ± 2282	1812 ± 400	1.7 ± 0.6
800 mg Comp X	5209 ± 1554	1045 ± 264	2.4 ± 1.0
800 mg Comp 8	12162 ± 3059	2143 ± 576	2.1 ± 0.8

[0076] Based on the mean ratios of $AUC_{(0-48\ h)}$-values the relative bioavailability of Composition 8 vs Composition X was estimated between 170% and 233%, depending on the dose administered (see following table).

Table

Relative bioavailability of Composition 8 vs. Composition X		
Dose of [mg]	Mean ratio of $AUC_{(0-48\ h)}$ Comp 8 vs. Comp X	Conversion Factor: Comp X vs. Comp 8
200	1.70	0.59
400	2.09	0.48
600	2.15	0.47
800	2.33	0.43

[0077] Conclusion: The composition according to the present invention (Composition 8) has a significantly higher bioavailability in humans be at least factor 1.7 when compared to the commercial form (Composition X).

[0078] The accompanying Figure III provides a graphical plot of the mean $AUC_{(0-48\ h)}$ - values of composition X (open triangles) versus those of Composition 8 (solid Circles). AUC-values (in ng.h/ml) of Ciclosporin vertically and dose horizontally as obtained from Example 4.

[0079] The extent of absorption of Composition 8 (in terms of $AUC_{(0-48\ h)}$-values) seemed to be independent of dose, whereas the extent of absorption of Composition X declined with increasing doses (see Figure III).

Claims

1. A trans-esterification product of corn oil and glycerol comprising predominately of linoleic acid and oleic acid mono-, di- and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product has been treated so as to

   a) reduce the saturated fatty acid component content of mono-, di- and tri-glycerides; and to
   b) enhance the unsaturated fatty acid component content of mono-, di- and tri-glycerides so that the linoleic acid ad oleic acid mono-, di- and tri-glyceride content is in total 85% by weight or more of the whole composition, and
   the product has a total palmitic acid and stearic acid content of mono-, di- and tri-gylcerides of less than 10% by weight.

2. A product as claimed in claim 1 having 30% to 40% by weight of mono-glycerides.

3. A product as claimed in claim 1 or claim 2 having 45% to 55% by weight of di-glycerides.

4. A product as claimed in any preceding claim having from about 7.5 to about 15 % by weight of tri glycerides.

5. A product as claimed in any preceding claim having a free glycerol content of less than 5% by weight.

6. A product as claimed in any preceding claim having a free glycerol content of less than 2% by weight.

7. A transesterification product of corn oil and glycerol having a saturated fatty acid content of mono-, di-, and tri-glycerides, and having a free glycerol content less than 10% by weight, which product comprises

i) from about 25% to about 50% by weight of mono-glycerides, from about 30% to about 60% by weight of di-glycerides, and at least 5% by weight of tri-glycerides; and
ii) a linoleic acid, oleic acid and linolenic acid mono-, di- and tri-glyceride content of at least 85% by weight;
wherein the total palmitic acid and stearic acid content of mono-, di-, and tri-glycerides is less than 10% by weight.

8. A product as claimed in claim 7 having 30% to 40% by weight of mono-glycerides.

9. A product as claimed in claim 7 or claim 8 having 45% to 55% by weight of di-glycerides.

10. A product as claimed in any one of claims 7 to 9 having from about 7.5 to about 15% by weight of tri-glycerides.

11. A product as claimed in any one of claims 7 to 10 having a free glycerol content of less than 5% by weight.

12. A product as claimed in any one of claims 7 to 11 having a free glycerol content of less than 2% by weight.

13. A process for obtaining a refined glycerol-transesterified corn oil according to any preceding claim, comprising heating of corn oil with glycerol at high temperature in the presence of a suitable catalyst under an inert atmosphere with continuous agitation to effect glycerol-transesterification, and refining said product by freezing procedures coupled with separative techniques.

14. A pharmaceutical composition comprising a product as claimed in any of claims 1 to 6.

15. Use of a product as claimed in any of claims 1 to 6 in a pharmaceutical composition.

16. A pharmaceutical composition comprising a product as claimed in any of claims 7 to 12.

17. Use of a product as claimed in any of claims 7 to 12 in a pharmaceutical composition.

Claims for the following Contracting States : GR, ES

1. A process for preparing a trans-esterification product of corn oil and glycerol which product comprises predominately of linoleic acid and oleic acid mono-, di- and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product has been treated so as to

a) reduce the saturated fatty acid component content of mono-, di- and tri-glycerides; and to
b) enhance the unsaturated fatty acid component content of mono-, di- and tri-glycerides so that the linoleic acid and oleic acid mono-, di- and tri-glyceride content is in total 85% by weight or more of the whole composition, and
the product has a total palmitic acid and stearic acid content of mono-, di- and tri-gylcerides of less than 10% by weight.

2. A process as claimed in claim 1 wherein the product contains 30% to 40% by weight of mono-glycerides.

3. A process as claimed in claim 1 or claim 2 wherein the product contains 45% to 55% by weight of di-glycerides.

4. A process as claimed in any preceding claim wherein the product contains from about 7.5 to about 15 % by weight of tri-glycerides.

5. A product as claimed in any preceding claim having a free glycerol content of less than 5% by weight.

6. A process as claimed in any preceding claim wherein the product contains a free glycerol content of less than 2% by weight.

7. A process for preparing a transesterification product of corn oil and glycerol which product comprises a saturated fatty acid content of mono-, di-, and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product comprises

i) from about 25% to about 50% by weight of mono-glycerides, from about 30% to about 60% by weight of di-glycerides, and at least 5% by weight of tri-glycerides; and
ii) a linoleic acid, oleic acid and linolenic acid mono-, di- and tri-glyceride content of at least 85% by weight; wherein the total palmitic acid and stearic acid content of mono-, di-, and tri-glycerides is less than 10% by weight.

8. A process as claimed in claim 7 wherein the product contains 30% to 40% by weight of mono-glycerides.

9. A process as claimed in claim 7 or claim 8 wherein the product contains 45% to 55% by weight of di-glycerides.

10. A process as claimed in any one of claims 7 to 9 wherein the product contains from about 7.5 to about 15 % by weight of tri-glycerides.

11. A process as claimed in any one of claims 7 to 10 wherein the product contains a free glycerol content of less than 5% by weight.

12. A process as claimed in any one of claims 7 to 11 wherein the product contains a free glycerol content of less than 2% by weight.

13. A process for obtaining a refined glycerol-transesterified corn oil according to any preceding claim, comprising heating of corn oil with glycerol at high temperature in the presence of a suitable catalyst under an inert atmosphere with continuous agitation to effect glycerol-transesterification, and refining said product by freezing procedures coupled with separative techniques.

14. A trans-esterification product of corn oil and glycerol comprising predominately of linoleic acid and oleic acid mono-, di- and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product has been treated so as to

a) reduce the saturated fatty acid component content of mono-, di- and tri-glycerides; and to
b) enhance the unsaturated fatty acid component content of mono-, di- and tri-glycerides so that the linoleic acid and oleic acid mono-, di- and tri-glyceride content is in total 85% by weight or more of the whole composition, wherein
the product has a total palmitic acid and stearic acid content of mono-, di- and tri-gylcerides of less than 10% by weight; 30% to 40% by weight of mono-glycerides, 45% to 55% by weight of di-glycerides, from about 7.5 to about 15 % by weight of tri-glycerides, and the free glycerol content is less than 2% by weight.

15. A pharmaceutical composition comprising a product as claimed in claim 14.

16. A transesterification product of corn oil and glycerol having a saturated fatty acid content of mono-, di-, and tri-glycerides, and having a free glycerol content less than 10% by weight, which product comprises

i) from 30% to 40% by weight of mono-glycerides, from 45% to 55% by weight of di-glycerides, and about 7.5% to about 15% by weight of tri-glycerides; and
ii) a linoleic acid, oleic acid and linolenic acid mono-, di- and tri-glyceride content of at least 85% by weight; wherein the total palmitic acid and stearic acid content of mono-, di-, and tri-glycerides is less than 10% by weight, and the free glycerol content is less than 2% by weight.

17. A pharmaceutical composition comprising a product as claimed in claim 16.

Fig. I